

Relationship of Hippuric Acid Excretion to Urinary Volume.*

PERITZ SCHEINBERG AND J. D. MYERS. (Introduced by E. A. Stead, Jr.)

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

There is disagreement in the literature in regard to the relationship between hippuric acid excretion and urinary volume. Machella and co-workers¹ have indicated that the amount of hippuric acid excreted in one hour following the injection of sodium benzoate increases as the urine volume rises. Probst and Londe,² on the other hand, using oral administration of sodium benzoate to 14 normal subjects found, by comparing one subject with another, that the amount of hippuric acid excreted was apparently independent of urinary volume. This interrelationship is of considerable clinical importance. In order for the present standards for the interpretation of the hippuric acid test of hepatic function, as it is commonly and widely used, to be valid, the amount of hippuric acid excreted should be independent of urine volume. This report deals with the effects of altering urinary volume in a given subject on the amount of hippuric acid excreted after a standard dose of sodium benzoate.

The intravenous one hour hippuric acid test was performed by the method of Quick,³ with the modifications suggested by Marron.⁴ Of the 9 subjects investigated, 3 were house-staff members, and the others were chosen because of the mildness of the disease for which they were hospitalized and the absence of evidence of liver disease. All of the procedures, including the analyses, were done by one of us (P.S.) in a uniform manner. A series of 3 tests was done on each subject on 3 consecutive days. In each instance, no food was taken for 6 hours prior to the determination. The urine volume was altered by vary-

ing the amount of water given to the subject prior to the test. Nausea was never encountered. The subjects were all young men who were allowed to empty their bladders completely while standing erect.

In order to check for impurities in the hippuric acid yields, the crystals in 5 cases were re-dissolved after weighing and titrated with 0.2 N sodium hydroxide, using phenolphthalein as indicator; in no instance was the difference between the results obtained by the gravimetric and the titrametric procedures greater than 0.03 g. As a further precaution, melting point determinations were done on 5 cases. These varied between 182.0°C and 186.0°C. The melting point for pure hippuric acid crystals is given as 187.5°C.

The results are given in Table I. The rate of urine excretion ranged between extremes of 1 and 15 ml per minute without any significant variation in the amount of hippuric acid excreted. In the low urine output group (0 to 2 ml per min.), the average amount of hippuric acid excreted was 1.48 ± 0.67 g. In the high urine output group (5 to 15 ml per min.), the average amount of hippuric acid excreted was 1.54 ± 0.66 g—a difference which falls within the range of experimental error. A medium urine output (2 to 5 ml per min.) was obtained on only 6 of the subjects; the average hippuric acid excretion in this group was 1.42 g.

The lack of correlation between hippuric acid excretion and urine volume suggests that hippuric acid is excreted by the renal tubules, for this independence from volume is one of the identifying characteristics of substances excreted by the tubules. The investigation of

* This work was supported by a grant from the Life Insurance Medical Research Fund.

¹ Machella, T. E., Helm, J. D., and Chornock, F. W., *J. Clin. Invest.*, 1942, **21**, 763.

² Probst, J. G., and Londe, S., *Ann. Surg.*, 1940, **111**, 230

³ Quick, A. J., Ottenstein, H. N., Weltehek, H., *Proc. Soc. Exp. Biol. and Med.*, 1938, **38**, 77.

⁴ Marron, T. U., *J. Lab. and Clin. Med.*, 1941, **27**, 108.

TABLE I. Hippuric Acid Excretion at Varying Urinary Volumes.

Subject	Diagnosis	Low urine output (0 to 2 ml/min.)		Medium urine output (2 to 5 ml/min.)		High urine output (5 ml/min. and above)	
		Urine vol. ml/hr	Hippuric acid excr. g/hr	Urine vol. ml/hr	Hippuric acid excr. g/hr	Urine vol. ml/hr	Hippuric acid excr. g/hr
P.S.	Normal	56 (a)	1.71			574	1.53
J.M.	"	97 (b)	1.50			658	1.37
A.T.	"	72	1.66	129	1.56	476	2.06
		61 (a)	1.90				
		67 (b)	2.02				
W.S.	Duodenal ulcer	80	0.95	295	1.29	675	1.09
K.C.	Lung abscess	57	0.79	175	0.98	865	0.86
L.Y.	CNS syphilis, fever therapy	72	1.15	225	1.15	575	1.58
J.E.	Rheumatoid arthritis	116	1.91	260	1.88	875	2.00
T.S.	Bysinosis	75	1.50	155	1.65	900	1.58
W.W.	Hysteria	60 (a)	1.76			600	1.76
		105 (b)	1.85				
		77	1.48 ± 0.67*	206	1.42 ± 0.71*	689	1.54 ± 0.66*
	Mean						

* Standard deviation.

Smith and co-workers,⁵ who showed that various hydroxy- and amino-substituted derivatives of hippuric acid are excreted by the renal tubules would support this view. The rapidity of excretion of hippuric acid into the urine⁶ is also in favor of its being so excreted by a tubular mechanism.

The independence of hippuric acid excretion and urinary volume would apply, of course, only to subjects with normal or moderately impaired renal function. The normal kidney has considerable reserve in the excretion of hippuric acid in the standard test, as Schwei and Quick⁶ have shown that the ability of the kidney to excrete hippuric acid is over 2.5 times as great as the speed of synthesis by the liver. Thus it is not unexpected that normal hippuric acid excretion will occur despite a diminished urea clearance and even in some instances of mild elevation of the blood urea. Theoretically, when renal damage is far advanced, active tubular excretion as well as reabsorption by the tubules of that hippuric acid filtered through the glomeruli would be markedly impaired. Then more hippuric acid could be eliminated in a large than in a small output of urine. That this situation does exist at times is suggested by the report of Snapper and Grunbaum⁷ in which patients with uremia did excrete more hippuric acid in larger volumes of urine.

Summary. The rate of excretion of hippuric acid is independent of urine volume, indicating that the present standards for the interpretation of the hippuric acid test are valid. It is suggested that hippuric acid excretion is a function of the renal tubules.

⁵ Smith, H. W., Finkelstein, H., Aliminos, T., Crawford, B., and Grober, M., *J. Clin. Invest.*, 1945, **24**, 388.

⁶ Schwei, G. P., and Quick, A. J., *Proc. Soc. Exp. Biol. and Med.*, 1942, **50**, 319.

⁷ Snapper, J., and Grunbaum, A., *Klin. Wchnschr.*, 1924, **3**, 101.